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Effects of Oral Contraceptive Usage on B₁₂ and Folate Levels

SUMMARY

Evidence shows a fall in folate and vitamin B₁₂ levels in women taking oral contraceptives. These levels do not return to normal until about three months after usage has stopped, but many women become pregnant during this time. This paper examines the evidence for an effect on such pregnancies of lowered folate and B₁₂ levels, and concludes that nutritional counselling should begin in schools, should continue in the medical care of women in their childbearing years, and folic acid supplementation should begin as soon as pregnancy is confirmed. This supplementation should be periconceptional in women at higher risk of bearing a child with neural tube defects, and greater in multiple pregnancy, malabsorption, hemolytic anemia and concomitant use of drugs known to be folate antogonists. (Can Fam Physician 1985; 31:1523-1525.)

SOMMAIRE

L'évidence accumulée révèle une diminution des niveaux de folate et de vitamine B₁₂ chez les femmes qui prennent des anovulants. Ces niveaux ne reviennent pas à la normale avant qu'il ne se soit écoulé trois mois après la cessation des anovulants, mais bien des femmes deviennent enceintes durant cette période. Cet article examine les preuves d'un tel effet sur les grossesses où les niveaux de folate et de B₁₂ sont diminués, et conclut que le counselling nutritionnel devrait débuter dans les écoles, se poursuivre au niveau des soins médicaux aux femmes en âge de procréer, et qu'un supplément d'acide folique devrait être initié dès la confirmation de la grossesse. Ce supplément devrait être plus important chez les femmes à haut risque de porter un enfant souffrant d'anomalie du tube neural, de grossesses multiples, de malabsorption, d'anémie hémolytique et faisant un usage concomitant de médicaments connus comme antagonistes du folate.

Key words: Oral contraceptives, vitamin B₁₂, serum folate

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THERE ARE NOW many reports of a fall in folate and vitamin B₁₂ levels in women taking contraceptive agents (OCs). With a normal diet, folate levels return to normal about three months after discontinuing OCs. Should a pregnancy ensue within six months of discontinuing OCs, there is a greater incidence of folate deficiency during the pregnancy than in those who had not taken OCs before becoming pregnant.²

In my practice many women become pregnant within three months of discontinuing the use of these drugs, despite advice to the contrary. This paper reviews the possible effects of oral contraceptives on vitamin B_{12} and folate levels, and discusses the attendant risks to the mother and the fetus if these vitamin levels drop and a pregnancy ensues before they are rectified.

Folate Levels in OC Users

There are many reports of an association between folate deficiency and the use of OCs³⁻⁵ Shojania⁵ showed that folate levels fell progressively with duration of OC usage. However, Castren⁶ and Paine,⁷ found no change in folate levels with time on steroid contraceptives. These findings, however, were not confirmed by others;7-9 in fact, Castren and Rossi⁶ reported a slight increase in the average folic acid level of 15 of 30 women after three months' treatment with OCs. I similarly found a rise in folic acid levels in OC users under age 25 (unpublished observations).

Clinical Effects of Low Folate Levels in The Non-pregnant Woman

Anemia

There are now several reports of megaloblastic anemia in users of contraceptive steroids.^{3, 4, 10-12}

Pregnancy predisposes to folate deficiency; Chanarin¹⁴ reported folic acid deficiency anemia in 2.1±1.5% of pregnancy in Britain, Eire, and Canada. Therefore, women who embark on a pregnancy soon after discontinuing OCs are likely at greater risk of folate deficiency and its complications.¹⁵ Martinez and Roe¹⁶ verified that women becoming pregnant within six months of discontinuing OCs had lower levels of serum and red blood cell folate than those who had not been taking birth control pills shortly before becoming pregnant.

Cervical Dysplasia

In 1973, Whitehead et al.¹⁷ observed megaloblastic features in cervi-

cal epithelial cells from a group of women using OCs. These women had no associated evidence of systemic folate deficiency, but the cytological changes were reversed with oral folate supplementation.

Butterworth et al. 18 showed that mean RBC folate concentration was lower among OC users than non-users (189 versus 269 ng/ml respectively, p<0.01) and even lower among users with dysplasia (161 versus 269 ng/ml respectively, p<0.001). They suggest that either a reversible localized derangement in folate metabolism may sometimes be misdiagnosed as cervical dysplasia, or such a derangement is an integral component of the dysplastic process and may be arrested, or possibly reversed, by folic acid supplementation.

Dental caries and dermatological evidence of malnutrition

Prasad et al.¹⁹ showed a decrease in serum folate and erythrocyte folate due to OCAs, mainly in an upper socioeconomic group of subjects. There was also an increase in abnormal clinical findings, indicating malnutrition, such as angular lesions of the mouth, dry skin and dry hair compared with a control group not taking OCs. The incidence of dental caries was increased in OC users in a higher socioeconomic group. These latter effects might be caused by a decreased plasma zinc concentration.²⁰

Mental function

In 1962 Herbert²¹ suggested that mental changes were a part of the clinical folate deficiency state.

Thornton²² demonstrated that hospitalized psychiatric patients have a higher prevalence of subnormal serum folate levels than do normal controls, regardless of sex or age. Further, the dietary ratings of the low serum folate patients did not differ from the normal folate level patients, so some other factor than diet must be at work.

Postpartum psychosis

Thornton²³ also describes the case of a young woman given no folate supplementation during pregnancy and who developed severe postpartum psychosis. She was found to have a macrocytic anemia with undetectable serum folate. Treatment with intramuscular folic acid was begun, and on

the tenth day of therapy, a complete remission occurred. There have however, been no other similar case reports.

Thus lowered folate levels associated with OC usage have been implicated in the etiology of megaloblastic anemia, cervical dysplasia, dental caries and several dermatological conditions. It seems unlikely, however, that any folate lowering due to the use of contraceptive steroids has resulted in clinical psychosis.

Clinical Effects of Low Folate Levels in Pregnant Women

There are many reports of complications from low folic acid levels in both mother and fetus. This lowered vitamin level could be due to a pregnancy beginning very soon after discontinuing OCs, ¹⁶ the effects of the pregnancy itself on maternal folate levels, ^{13, 14} celiac disease in the mother, or maternal use of other drugs known to lower folate levels such as diphenylhydantoin, alcohol, barbiturates, colchicine and numerous drugs used in cancer chemotherapy. ²⁴

Hazards to the mother and fetus in the absence of frank anemia are controversial but include the following:

Restless leg syndrome

Botez²⁵ has suggested a correlation between this syndrome in pregnancy and folate deficiency.

Hydatidiform mole

Reynolds²⁶ advances the thesis that hydatidiform mole may be partly due to folate deficiency.

Toxemia of pregnancy

In 1967 Stone²⁷ and coworkers implicated folate deficiency in toxemia of pregnancy.

Late pregnancy bleeding

That bleeding late in a pregnancy may be partly due to low folate levels has been postulated by Streiff.²⁸

Abortion, recurrent abortion and abruptio placentae

Hibbard and others ²⁹⁻³¹ have suggested that low folate levels are at least partly responsible for some abortions and abruptio placentae. This work, however, has been discredited because they used the formiminoglutamic acid

test (FIGLU) for folate, which is not specific enough.

Folate deficiency in the newborn

In a study of 100 women at risk for nutritional deficiencies, Blot et al. 32 found that though there was no difference in hemoglobin and RBC indices between infants born of iron or folate deficient mothers and others, there was a significant correlation between mother and newborn serum folate (p<0.001) and RBC folate values (p<0.001).

Neural tube defects (NTDs)

Smithells and associates33 found that first trimester RBC folates and WBC vitamin C levels were significantly lower in six mothers who gave birth to infants with NTDs when compared to controls. This same group were able to reduce an expected incidence of recurrence of NTD in infants from 5% to 0.6% by giving mothers planning a pregnancy a prophylactic preparation containing folic acid. Further, in mothers who had already given birth to more than one affected child. the expected recurrence rate of 11.5% was reduced to zero.34 There are similar studies by Laurence and coworkers. 35-37 However, these trials were very small and the effect of diet and other ingested vitamins cannot be excluded from the folate effect. Both Smithells and Laurence have recommended larger trials.

Other congenital defects

Folate deficiency has been implicated in other fetal malformations. ^{38, 39} In a study by Blot, ³² the mothers of two infants with hare lip and cardiopathy exhibited low folates and low ferritin values. Other workers have been unable to demonstrate any relationship between malformations and folate deficiency. ⁴⁰⁻⁴²

Mental retardation

The evidence relating folate deficiency in pregnancy to mental retardation and other defects in the central nervous system function and development is reviewed by Herbert and Tisman. 43

Small for dates (retarded fetal growth)

Elliot⁴⁴ related retarded fetal growth to maternal folate deficiency. In a

prospective study of 805 women seen early in pregnancy, Hibbard⁴⁵ demonstrated a markedly increased rate of small-for-dates infants whose mother had low folate levels early in the pregnancy.

Premature delivery

In his study of 100 women at risk for nutritional deficiencies in pregnancy Blot³² found the duration of pregnancy was shorter than normal in women with low folate but of similar duration in iron deficient and non iron deficient women.

In a previous study, this same group⁴⁶ showed that folate supplementation increased pregnancy duration by approximately one week and that the increase in newborn height and weight might be explained by longer gestation.

However, Pritchard et al.47 examined fetal health and wastage in women who were taking OCs before pregnancy and found no difference from the control population. In a prospective study of 163 pregnant girls under age 16, Daniel and coworkers⁴⁸ found no increase in prematurity of infants born to girls with subnormal folates as compared to those of girls with normal folates. None of the patients had third trimester bleeding, abruptio or malformations, although 90.4% of the girls took less than 50% of the recommended diet allowance and 52% of the girls took less than 10% of the recommended levels of folate.

The suggestion that prophylactic folic acid administration would reduce the incidence of pregnancy complications of abortion, abruptio placentae, preterm delivery and congenital malformations has not been confirmed. 49, 50

In summary, there is much conflicting evidence that maternal folate deficiency is implicated in many pregnancy complications and neonatal pathology. Undoubtedly poor general nutrition is partly responsible for intrauterine growth retardation and prematurity, with attendant risks to the infant.

Effects of OC Usage on Vitamin B₁₂ Levels

Prasad et al.⁵¹ found no change in serum vitamin B_{12} levels in users of contraceptive steroids in a high socioeconomic group but there are several

reports of reduced serum B_{12} levels in OC users. $^{52, 53, 55}$ However, Schilling tests carried out in four subjects with low serum B_{12} levels were normal, 12 indicating that combined OCs did not impair absorption of this compound.

Further, in a study of 20 women taking OCs for two to 60 months, Wertalik et al.⁵³ showed that though the mean serum B_{12} level was 40% lower than in controls, the mean unsaturated B_{12} binding capacity was unchanged. Further, although 15% of the subjects were clearly in the deficient range ($<100 \, \mu\mu g/ml$), one subject having a B_{12} level of 14, and the other $22 \, \mu\mu g/ml$, none had anemia or macrocytosis.

Many women will therefore demonstrate lowered serum vitamin B_{12} levels without associated fall in tissue levels or disease. Serum vitamin B_{12} levels in OC users should therefore only be measured if there is a macrocytosis on the peripheral smear or a raised mean corpuscular volume (MCV). Should a lowered serum vitamin B_{12} be found, other causes such as malabsorption syndrome, Crohn's disease, pernicious anemia and decreased intake as in vegans⁵⁵ must be considered.

Recommendations

Until more is known of the part played by vitamin B₁₂ and folate deficiency in the etiology of pregnancy and neonatal mishaps, the following are recommended:

- 1. As suggested by Laurence,⁵⁷ advice on diet should be part of the health education program at school.
- 2. Physicians should continue the counselling begun in the schools to all women in the childbearing age group, especially those taking OCs.
- 3. Periodically all women taking OCs should have their hemoglobin, MCV and a peripheral blood smear examined. A serum B_{12} and RBC folate level should be done only if anemia or macrocytosis is demonstrated.
- 4. Should the folate or B_{12} level of an OC user be low, other causes than the contraceptive—such as malabsorption, pernicious anemia and usage of other drugs—should be sought and appropriate action taken.
- 5. Folic acid supplementation should be recommended as soon as a pregnancy is diagnosed.
- 6. Until more is known about the etiology of neural tube defects, periconcep-

tional folic acid should be considered for all women who have already given birth or aborted fetuses with NTD, since the neural tube closes at eight weeks.

7. Patients with a multiple pregnancy, malabsorption, hemolytic anemia and those using drugs known to be folate antagonists will need greater supplementation.

Finally, I feel two quotations are worthy of note:

"In many cases it seems that misfortune arises when adverse environmental factors act on a constitutionally susceptible mother and fetus". 45

"It seems improbable that folate deficiency is ever an isolated cause of congential defect in the human being, but it may prove to be one correctable factor involved in malformations of multifactorial origin". 58

References

- 1. Shojania A, Hornady G, Barnes P. The effects of oral contraceptives on folate metabolism. Am J Obstet Gynecol 1971; 111:782-91.
- 2. Shojania A. Effect of oral contraceptives on vitamin B12 metabolism. Lancet 1971; 11:932.
- 3. Streiff R. Folate deficiency and oral contraceptives. JAMA 1970; 214:105-8.
- 4. Ryser J, Farguet J, Petite J. Megaloblastic anemia due to folic acid deficiency in a young woman on oral contraceptives. Acta Haematol (Basel) 1971; 45:319-24.
- 5. Shojania A, Hornady G, Barnes P. Oral contraceptives and serum folate level. Lancet 1968; 1:1376-7.
- 6. Castren O, Rossi R. Effect of oral contraceptives on serum folic acid content. Br J Obstet Gynaecol, 1970; 77:548-50.
- 7. Paine C, Grafton W, Dickson V, Elchner E. Oral contraceptives, Serum folate and hematologic status. JAMA 1975; 231:731-3.
- 8. Stephens M, Craft I, Peters T, Hoffbrand A. Oral contraceptives and folate metabolism. Clin Sci 1972; 42:405-414.
- 9. McLean F, Heine M, Held R, Streiff R. Relationship between oral contraceptives and folic acid metabolism. Am J Obstet Gynecol 1969; 104:745-7.
- 10. Lewis FB. Folate deficiency due to oral contraceptives. Minn Med 1974; 945-6.
- 11. Paton A. Oral contraceptives and foliate deficiency. Lancet 1969; 1:418.
- 12. Flury R, Angehrn W, Schweiz. Fulsauremangelanamie infolge einnahme oraler kontrazptiva. Med Wochenschr 1972; 102:1628-29.
- 13. Solomons E, Lee S, Wasserman M, Malkin J. Association of anemia in pregnancy and folic acid deficiency Br J Obstet Gynaecol 1962; 69:724-8.
- 14. Chanarin I. The megaloblastic anemias. Oxford: Blackwell Scientific Publication, 1979.
- 15. Pritchard J, Scott D, Whalley P. Maternal folate deficiency and pregnancy wastage. IV. Effects of folic acid supple-



PRESCRIBING SUMMARY

INDICATIONS: The treatment of the following infections caused by Strept. pyogenes, Strept. pneumoniae, Staphy-lococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains), E. Coli, Proteus mirabilis, Klebsiella pneumoniae, H. Influenzae (including ampicillin-resistant strains):

- Ottis media, Lower Respiratory Infections, including pneumonia, bronchitis, and pulmonary complications resulting from
- Upper Respiratory Infections, including pharyngitis and

4. Skin and Soft-Tissue Infections,
5. Urinary Tract Infections.

CONTRAINDICATIONS: Persons who have shown hypersensitivity to the cephalosporin antibiotics

WARNINGS: Cephalosporins should be given only with caution to penicillin-sensitive patients. There is some evidence of cross-allergenicity between penicillins and cephalosporins. Patients have been reported to have had cepinalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both. Administer with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Ceclor occurs, the drug should be discontinued and the patient treated with the usual agents. Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics; therefore, it is important to consider its diagnosis in patients who lop diarrhea in association with the use of antibiotics.

PRECAUTIONS: Safety during pregnancy has not been established. Small amounts of Ceclor have been detected established. Small amounts of vector nave been detected in mother's milk following administration of single 500 mg doses. The effect on nursing infants is not known. Caution should be exercised when Cector is administered to a nursing woman. Prolonged use may result in the overgrowth of non-susceptible organisms. If super-infection occurs, administration of Cector should cease and approoccurs, administration of Oeclor should cease and appropriate measures taken. Positive direct Coombs' tests have been reported during treatment with cephalosporins and may be due to the drug. Administer with caution in the presence of markedly impaired renal function. The safe dosage is likely to be lower than that usually recommended. A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP).

ADVERSE REACTIONS: Of 1,493 patients treated with cefaclor, 87 (5.8%) had adverse reactions or abnormal ceraciot, 37 (3.8%) had adverse reactions or abnormal laboratory values judged to be drug-related. These included: nausea and vomiting, dyspepsia, diarrhea, rash (including urticara & morbilliform eruptions), positive Coombs; eosinophilia, epintal moniliasis, vaginitis, elevated SGOT, and elevated SGPT. Other adverse reactions evanigated these fresheaths includer servicing. reactions experienced less frequently include: pruritus, dizziness, headache, somnolence, abdominal pain, leg cramps, abnormal taste, and fever. Leukopenia, decreased hemoglobin and hematocrit, neutrophilia, elevated alkaline phosphatase, lymphocytosis, lympho-cytopenia, thrombocytosis, elevated BUN and creatinine hematuria and pyuria have also been reported. Cases of serum-sickness-like reactions (including skin manifestations, fever and arthralgia/arthritis), anaphylaxis, and pseudomembranous colitis have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: There has been no experience of overdosage with Ceclor. If a large overdose has been recently consumed, the patient should be kept under observation and appropriate treat-ment undertaken as considered necessary.

DOSAGE AND ADMINISTRATION: Ceclor is administered

orally.

Adults—The usual adult dosage is 250 mg every 8 to 12 hours. The maximum recommended dosage is 2 g per

hours. The maximum recommended dosage is 2 g per day, although doses of 4 g per day have been administered safely for 28 days.

Children—The usual dosage for children is 20 mg/kg/day in divided doses every 8 to 12 hours. In more serious infections, otilis media, and those infections caused by the servation of the company of the property of the prop

less susceptible organisms, 40 mg/kg/day is recommended, up to 1 g per day. For lower respiratory tract infections, the total daily dosage should be divided and administered 3 times daily. For B-hemolytic streptococcal infections administer for at least ten days.

DOSAGE FORMS:

Ceclor 250 mg Pulvules 3061. Each opaque purple and white capsule contains 250 mg cefaclor. Bottles of 100

Ceptor 500 mg Pulvules 3062. Each opaque purple and grey capsule contains 500 mg cefaclor. Bottles of 30 and 100 capsules.
Ceclor 125 mg for Oral Suspension (M-5057). Strawberry flavored, 125 mg/5 ml..
Ceclor 250 mg for Oral Suspension (M-5058). Grape

flavored, 250 mg/5 mL.

Reconstitute suspensions by adding 60 mL of water to each 100 mL bottle or 90 mL for each 150 mL bottle in two portions. Shake well after each addition. After mixing, store in a refrigerator. The mixture may be kept for 14 days without significant loss of potency. Shake well before using. Keep tightly closed.

Product Monograph available on request



Eli Lilly Canada Inc., Toronto, Ontario. & Licensed user of trademarks owned by Eli Lilly and Company ments, anti-convulsants and oral contraceptives. Am J Obstet Gynaecol 1971; 109:341-6.

16. Martinez O, Roe D. Effect of oral contraceptives on blood folate levels in pregnancy. Am J Obstet Gynaecol 1977; 128:255-61.

17. Whitehead R, Reyner F, Lindenbaum J. Megaloblastic changes in the cervical epithelium: Association with oral contraceptive therapy and reversal with folic acid. JAMA 1973; 226:1421-4.

18. Butterworth CE Jr, Hatch KD, Gore H, Mueller H, Krumdieck C. Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. Am J Clin Nut 1982; 35:73-82.

19. Prasad A, Lei K, Oberleas D, Moghissi KS, Stryker J. Effect of oral contraceptive agents on nutrients: II. Vitamins. Am J Clin Nutr 1975; 28:385-91.

20. Liu F, Liu S. Effect of contraceptive steroids norethynodrel and mestranol on dental caries activity in young adult female rats. J Dent Res 1973; 52:753-7.

21. Herbert V. Experimental nutritional folate deficiency in man. Trans A Assoc Amer Physicians 1962; 75:307-20.

22. Thornton W. Thornton B. Folic acid, mental functions and dietary habits. J Clin Psychiatry 1978; 39:315-9

23. Thornton W. Folate deficiency in puerperal psychosis. Am J Obstet Gynaecol . 1977; 129:222-3.

24. Stebbins R, Scott J, Herbert V. Drug induced megaloblastic anemias. Semin Hematol 1973; 10:235-51.

25. Botez M. Folate deficiency and neurological disorders in adults. Med Hypotheses 1976: 2:135-40.

26. Reynolds S. Hydatidiform mole; a vascular congenital anomaly. Obstet Gynecol 1976; 47:244-49.

27. Stone M, Lugby A, Feldman R, Gordon M, Copperman J. Folic acid metabolism in pregnancy. Am J Obstet Gynaecol 1967; 99:638-48

28. Streiff R, Little A. Folate deficiency in pregnancy. N Engl J Med 1967; 276:776-

29. Hibbard B, Hibbard E, Jeffcoate T. Folic acid and reproduction. Acta Obstet Gynecol Scand 1965; 44:375-400.

30. Hibbard BM, Hibbard ED. Aetiological factors in abruptio placentae. Br Med J 1963; 11:1430-6.

31. Hibbard BM, Jeffcoate T. Abruptio placentae. Obstet Gynecol 1966; 27:155-

32. Blot I, Rey A, Kaltwasser JP, Francoual J, Paprernik E, Tchernia G. Folate and Fe deficiencies in mothers and their newborn children. Blut 1982; 44:297-303. 33. Smithells R, Sheppard S, Schorah C. Possible prevention of neural NBE defects by periconceptual vitamin supplement. Árch Dis Child 1976; 51:944-50

34. Smithells R, Sheppard S, Schorah C, et al. Vitamin deficiency and neural tube defects. Lancet 1980; 1:339-40.

35. Laurence KM, James N, Campbell H. Quality of the diet and blood folate levels. Br Med J 1982; 285:216.

36. Laurence KM, Jones N, Miller M, et al. Double blind randomised trial of folate treatment before conception to prevent recurrence of NTD. Br Med J 1981; 282:1509-11.

37. Laurence KM, Campbell H. Trial of folate treatment to prevent recurrence of NTD. Br Med J 1981; 282:2131

38. Fraser J, Watt H. Megaloblastic anemia in pregnancy and the puerperium. Am J Obstet Gynaecol 1964; 89:532-5.

39. Hibbard E, Smithells R. Folic acid metabolism and human embryopathy. Lancet 1965; 1:1254

40. Gites C. J Clin Pathol 1966; 191-11. 41. Pritchard J, Scott D, Whalley P, Haling R Jr. Infants of mothers with megaloblastic anemia due to folate deficiency. JAMA 1970; 211:1982-84

42. Scott D, Whalley P, Pritchard J. Maternal folate deficiency and pregnancy wastage. Obstet Gynecol 1970; 36:26-8. 43. Herbert V, Tisman G. In: Gaull, G. ed. Effects of deficiencies of folate acid and vitamin B12 on central nervous system func-

tion and development. Biology of brain dysfunction. New York and London: Plenum, 1973; 1:373-92.

44. Elliott, P. Int J Gynaecol Obstet 1970; 8:265

45. Hibbard BM. Folates and the fetus. S Afr Med J 1975; 49:1223-6.

46. Blot I, Papiernik E, Koltwasser JP, Werner E, Tehernia G. Influence of routine administration of folic acid and iron during pregnancy. Gynecol Obstet Invest 1981; 12:294-304.

47. Pritchard J, Scott D, Whalley P. Molmol folate deficiency and pregnancy wastage. J Obstet Gynaecol 1971; 109:341-6. 48. Daniel W. Mounger J, Perkins TC. Obstetric and fetal complications in folate deficient adolescent girls. Am J Obstet Gynecol 1971; 111:233-8

49. Whalley PJ, Scott DE, Pritchard JA. Maternal folate deficiency and pregnancy wastage I. Placental abruption. Am J Obstet Gynaecol, 1969; 105:670-78.

50. Fleming AF, Martin JD, Stenhouse NS. The relationship of maternal anemia and folate deficiency to uterine hemorrhage during pregnancy and fetal manformation. Aust NZ J Obstet Gynaecol 1975; 14-8.

51. Prasad A, Lei K, Oberleus D, Moghissi K. Stryker J. Effect of oral contraceptive agents on nutrients: 11 vitamins. Am J Clin Nutr 1975, 28:385-91

52. Briggs M, Briggs M. Endocrine effects on serum vitamin B12. Lancet 1972; 11:1037.

53. Wertalik L, Metz E, Lobuglio A, Blacerzak S. Decreased serum B12 levels with oral contraceptive use. JAMA 1972; 221:1371-4.

54. Davids R, Smith B. Pyridoxal, vitamin B12 and folate metabolism in women taking oral contraceptive agents. S Afr Med J 1974; 48:1937-40.

55. Shojania A. Oral contraceptives: effects on folate and vitamin B12 metabolism. Can Med Assoc J 1982; 126:244-6.

56. Roberts PD et al: Vitamin B12 states in pregnancy among immigrants to Britain. Br Med J 1973; 3:67-72.

57. Lawrence K, James N, Miller M, Campbell H. Increased risk of recurrence of pregnancy complicated by fetal neural tube defects in mothers receiving poor diets and possible benefit of dietary counselling. Br Med J 1980; 21:1592-4.

58. Smithells R. Environmental teratogens of man. Br Med Bull 1976; 32:27-33.